Early Communication about an Ongoing Data Review for Ezetimibe/Simvastatin (marketed as Vytorin), Ezetimibe (marketed as Zetia), and Simvastatin (marketed as Zocor)

This communication is based on information that FDA has not yet fully evaluated. FDA is not advising health care professionals to discontinue prescribing these products. FDA is considering, but has not reached a conclusion about whether this information warrants any regulatory action. FDA intends to update this document when additional information or analyses become available.

On January 14, 2008, Merck/Schering Plough Pharmaceuticals issued a Press Release reporting preliminary results from the Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) trial. This trial was designed to evaluate the amount of atherosclerotic plaque in blood vessels located in the neck based on images obtained through ultrasound in patients treated with Vytorin (ezetimibe plus simvastatin) or simvastatin alone. Merck/Schering Plough Pharmaceuticals, the company that conducted the trial, stated that there was no significant difference between Vytorin and simvastatin in the amount of atherosclerotic plaque in the inner walls of the carotid (neck) arteries despite greater lowering of LDL-cholesterol (bad cholesterol) with Vytorin compared to simvastatin. FDA has not received a final study report and at this time it is not clear why the lower levels of LDL cholesterol in the patients who took Vytorin did not lead to lesser amounts of plaque compared to patients treated with simvastatin alone.

ENHANCE was a 2-year, multi-national, randomized, double-blind study conducted in 720 patients with heterozygous familial hypercholesterolemia (HeFH), a condition that is associated with very high cholesterol levels and affects approximately 0.2 percent of the population. Half of the patients were treated with 10 mg of ezetimibe combined with 80 mg of simvastatin and half with 80 mg of simvastatin alone.

An elevated LDL-cholesterol level is an established risk factor for heart disease and many studies have supported the conclusion that lowering cholesterol levels reduces the risk for heart attack and stroke. Ezetimibe inhibits the absorption of cholesterol in the intestine and is approved to lower LDL-cholesterol levels. Simvastatin (Zocor) is a lipid-lowering agent (“statin”) approved to reduce LDL and increase high-density lipoprotein (HDL) (good) cholesterol levels and reduce the risk of cardiovascular events such as heart attack and stroke. Vytorin is approved for reducing LDL and increasing HDL cholesterol levels.

There are no clinical studies available that demonstrate a reduction in risk of heart attack or stroke when ezetimibe is used alone or in combination with a statin, including the fixed-dosed

combination drug of ezetimibe and simvastatin, Vytorin. While the overall incidence of cardiovascular events in ENHANCE was similar in both the ezetimibe/simvastatin and simvastatin-alone groups, there were not enough patients in this study to reliably test whether treatment with ezetimibe/simvastatin compared with simvastatin alone reduces the risk of cardiovascular events. An ongoing trial known as IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) is examining this question in 12,500 patients and will likely be completed in 2011. Physicians and patients should carefully consider the available data and current labeling for Zetia and Vytorin as they make individual treatment decisions.

This early communication is in keeping with FDA's commitment to inform the public about ongoing postmarketing drug issues. Once Merck/Schering Plough Pharmaceuticals completes the analysis of the unblinded data from ENHANCE, it will submit a final study report to FDA. Once FDA receives the final study report, FDA estimates it will take approximately 6 months to fully evaluate the data. After reviewing the data from the ENHANCE study, and considering all other available information about the link between LDL lowering and reduction of cardiovascular events, FDA will determine whether any further regulatory action is warranted with regard to Zetia and Vytorin and also whether any changes to FDA's current approach to drugs that lower LDL cholesterol are warranted.

Patients should talk to their doctors if they have any questions about the information from the ENHANCE trial.

The FDA urges both healthcare professionals and patients to report side effects from the use of ezetimibe to the FDA's MedWatch Adverse Event Reporting program

- online at www.fda.gov/medwatch/report.htm;
- by returning the postage-paid FDA form 3500 available in PDF format at www.fda.gov/medwatch/getforms.htm to 5600 Fishers Lane, Rockville, MD 20852-9787;
- faxing the form to 1-800-FDA-0178; or
- by phone at 1-800-332-1088

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